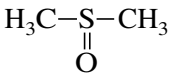
Dimethyl sulfoxide H

Classification/MAK value	**not yet established see Section II b MAK List 1990**
Synonyms:	methyl sulfoxide methylsulfinylmethane DMSO
Chemical name (CAS):	sulfinylbismethane
CAS number:	67-68-5
Structural formula:	
Molecular formula:	C_2H_6OS
Molecular weight:	78.1
Melting point:	18.55 °C
Boiling point:	189 °C
Vapour pressure at 20 °C:	0.6 hPa
1 ml/m³ (ppm) ≈ 3.24 mg/m³	**1 mg/m³ ≈ 0.309 ml/m³ (ppm)**

1 Toxic Effects and Modes of Action

Dimethyl sulfoxide (DMSO) is a colourless, odourless, aprotic, polar, highly hygroscopic liquid with a slightly bitter taste. DMSO mixes with water in an exothermic reaction. DMSO is also miscible with alcohols, acetone, chloroform, ethers and other organic solvents [1]. The excellent skin penetration of DMSO has long been known and used to improve the dermal absorption of Pharmaceuticals. Because of its radical trapping properties, DMSO is an anti-inflammatory agent. In pharmacological model systems, DMSO has been shown to have marked diuretic effects (like those of mannite), weak analgesic effects [2] and an indirect cholinergic effect (AChE inhibition) [3]. Since DMSO increases the skin penetration of organophosphates, for example, super-additive effects are to be expected in combined exposures [2].

Skin contact, especially with the undiluted substance, results in perceptible hyperthermia because of the heat of solution of DMSO in water (atmospheric humidity and water in deeper skin layers) and local vasodilation. Repeated skin contact leads to erythema, oedema, pruritis, hardening of the skin and scale formation [4].

Allergic reactions have been described occasionally. DMSO can increase the absorption of allergens through the skin [5, 6].

After rapid skin absorption, some of the DMSO is reduced to dimethyl sulfide which is exhaled (garlic-like foetor). The dimethyl sulfide which is not eliminated via the lungs is oxidized back to DMSO. Then, like the DMSO which was not reduced, it is oxidized to $DMSO_2$ (dimethyl sulfone) and excreted in the urine. The elimination is biphasic with half-lives of 11 to 14 hours (DMSO) and 60 to 70 hours ($DMSO_2$) [7].

The acute toxicity resulting from oral, dermal or parenteral intake of DMSO is very slight. The main effects of very high doses administered to experimental animals by intravenous injection are morphological and functional liver and kidney changes. Long-term oral or dermal administration also produces only slight toxicity. Typical findings in experimental animals include increased diuresis and damage to liver and kidney. To produce similar changes in inhalative exposures, together with pneumonia, it is necessary to vaporize very large quantities of DMSO.

Hepatotoxicity and nephrotoxicity have not been described in man. Urine findings are limited to haemoglobinuria after intravenous treatment with 1 g/kg during 3 days. This was caused by intravenous haemolysis as a result of injection of hyper-osmolar solutions. DMSO changes the refractive power of the lens. Prolonged treatment of animals leads to increased central opalescence and reduction in focal length of the central section of the lens, sometimes even to the development of a lens with two focal points. Species in which such lens alterations readily develop include the dog and small laboratory rodents. Controlled studies of persons receiving DMSO by long-term dermal application yielded no evidence of lens changes [8, 9].

There are no published studies of the reproductive toxicology of DMSO after inhalative exposure of animals. Embryotoxic and teratogenic effects of extremely high doses of orally and parenterally administered DMSO have been described.

There are numerous genotoxicity studies available. Since DMSO is used worldwide as a solvent for poorly water-soluble substances in the Ames test it is also tested in parallel as solvent control. No increase in the number of mutants is seen with DMSO. The results of other tests for point mutations (in bacteria, yeasts and mammalian cells) are not consistent. Chromatid breaks have been described after parenteral application of DMSO to rats. It is probably an unspecific effect which leads to the DNA single strand breaks induced in the mouse kidney.

Carcinogenic effects of DMSO have not yet been described. It is, however, possible that DMSO could increase the dermal absorption of other substances which are carcinogenic.

1.1 Pharmacokinetics

DMSO is absorbed very rapidly and almost completely through human skin and subsequently either excreted in the urine or metabolized [10]. In the liver and the kidney it is converted to dimethyl sulfide (DMS) by a sulfide reductase (see Figure 1). About 10 % of a dose applied dermally to man is eliminated by exhalation. The exact proportion of the dose converted to DMS by reduction is, however, unknown because the DMS is rapidly oxidized back to DMSO and $DMSO_2$ by mixed function oxidases.

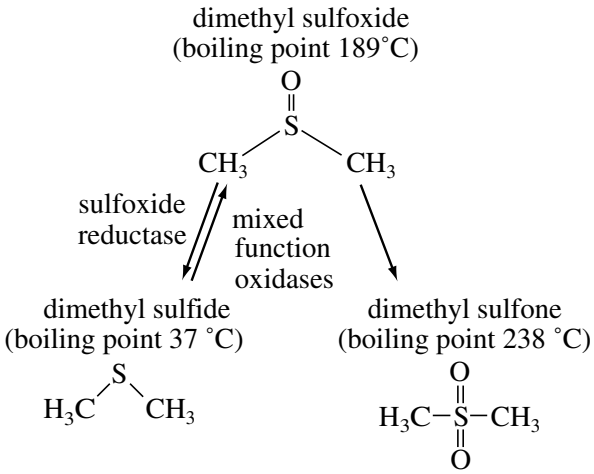


Figure 1. Breakdown products of dimethyl sulfoxide found in man

DMSO and $DMSO_2$ are found in the urine of exposed persons. The half-life of DMSO in man is between 11 and 14 hours, that of $DMSO_2$ between 60 and 70 hours [7].

The pharmacokinetics of DMSO in rhesus monkeys was studied during and after 14 days oral administration of the substance. The enteral absorption of DMSO is also rapid. A steady state is achieved after one day. The substance is no longer detectable 72 hours after the last dose. DMSO has a half-life of 16 hours in serum. $DMSO_2$ appears in the blood after 2 hours and reaches a steady state level on treatment day 4. Its half-life in blood is 38 hours and it can no longer be detected there 120 hours after the last dose. About 60 % of an orally administered dose is excreted in the urine as DMSO and about 16 % as $DMSO_2$ Neither DMSO nor $DMSO_2$ can be detected in faeces. The pulmonary elimination of DMS was not quantified in this study but was detected as a sweet smell in the exhaled air [11].

2 Effects in Man

Dermal exposure to DMSO causes skin reactions, erythema and pruritis, which are seen immediately after contact with the undiluted substance; 70 % solutions are usually tolerated without symptoms. In very sensitive individuals, however, reactions have been seen after contact with 10 % solutions. The skin reaction to the undiluted substance is put down to the hygroscopic properties of DMSO, on the one hand, and to the exothermic dissolving process on the other [4].

In a controlled study, 1 g of a gel containing 80 % DMSO was applied to the skin of 78 persons daily for two weeks. In addition to the skin reactions described above, sedation developed in 52 % of the treated persons, headaches in 42 %, sleepiness in 18 % and nausea in 32 %. In no case were there any changes in the eyes [8].

The absence of effects on the eyes after long-term dermal DMSO treatment has been reported in several studies [9].

3 Effects on Animals

3.1 Acute toxicity

The results of studies on the *acute* toxicity of DMSO are summarized in Table 1.

Rats survived inhalation exposure to DMSO under the following conditions:

2900 mg/m^3 for 24 hours
2000 mg/m^3 for 40 hours and
200 mg/m^3 7 hours daily for 30 days.

Pulmonary oedema was found in all exposed animals [15]. There were no sex-specific differences in toxicity. Characteristic was the garlic-like odour of the air exhaled by the animals. Other findings included reduced motility and reflexes, stupor, hypothermia, tremor, convulsions and reduced respiration rates. Haematuria and haemoglobinuria are observed after intravenous, subcutaneous or intraperitoneal administration of DMSO.

Table 1. LD_{50} values in g/kg body weight in various species

Species	Application route				Ref.
	dermal	p.o.	i.v.	s.c.	
mouse	50	21–28	4–9	15–25	[12, 13]
rat	40	15–28	5–8	12.9	[12, 13]
dog	> 11	>10	2.5		[13, 14]
monkey	> 11	> 4	4		[13]

3.2 Subchronic and chronic toxicity

The results of studies in which DMSO was administered orally or dermally to various species are shown in Table 2.

There is very little information as to the effects of inhalation of DMSO. Rabbits inhaled 25 or 50 ml DMSO-mist per hour, initially 1 hour daily for 5 weeks. Then after a two week recovery period, a three week re-exposure was followed by a five month recovery period. At the higher concentration the findings were pneumonia and "liver and kidney toxicity", at the lower concentration fatty infiltration of the liver and round-cell infiltration in the lungs [21].

3.3 Local effects on skin and mucous membranes

No effects were seen in nude mice after dermal application of the undiluted substance twice weekly for 3 weeks [22]. In rats immersed daily in 40–80 % solutions, punctate epidermal necrosis was first seen after 3 weeks; the severity of the lesion increased with increasing concentration [18]. Treatment of guinea pigs with the undiluted substance for 28 days produced neither macroscopic nor histopathological changes [22].

Table 2. Systemic effects of dimethyl sulfoxide after medium and long term oral or dermal application

Species	Dose	Duration	Findings	Ref.
p.o. application				
mouse	from 2.5 g/kg	6 weeks	– growth delayed, liver degeneration, tubulonephritis	[16]
rat	3–9 ml/kg	2 weeks	– growth delayed, increased diuresis	[17]
	from 5 ml/kg	13 weeks	– increased mortality, leukopenia, especially lymphopenia	[17]
	9 ml/kg	from 24 weeks	– effects on the lens	[18]
	9 ml/kg	52 weeks	– erosion in gastrointestinal tract, splenic atrophy, renal tubular dilation	[15,17]
dog	9 ml/kg	10 weeks	– tremor, increased water intake and diuresis	[18]
	1–9 ml/kg	16 weeks	– increased diuresis	[18]
	9 ml/kg	4 weeks	– haemoconcentration	[18]
	4.5 ml/kg	36 weeks	– haemoconcentration	[18]
	from 9 ml/kg	17 weeks	– milky opalescence of the lens centre	[3]
	from 3 ml/kg	51 weeks	– optical heterogeneity in the vitreous body	[18]
	7.5 ml/kg	16 weeks	– renal tubulus dilation, atrophy of epithelial and gland cells in the gastric mucosa	[18]
monkey	5 ml/kg	2–3 weeks	– diarrhoea, myopia, increased diuresis, lens changes	[18]
	3 ml/kg	14 weeks	– lens changes	[19]
	5 ml/kg	34 weeks	– tubulus changes with renal hyperaemia	[18]
dermal application				
rat	40–80 %*	26 weeks	– body weight, thymus and liver weight decreased, adrenal weight increased	[18]
rabbit	50 %, 90 %			[3]
	from 4 ml/kg	9 weeks	– lens changes	
	from 1 ml/kg	11 weeks	– lens changes	[20]
dog	60–100%			[18]
	10 ml/kg	7 weeks	– myopia	
	3 ml/kg	10 weeks	– myopia	
	10 ml/kg	12 weeks	– lens opacity	
	3 ml/kg	23 weeks	– lens opacity	
pig	50–90 %			[18]
	4 ml/kg,	52 weeks	– body weight gain delayed	
	0.75 ml/kg 90 %	55 weeks	– slight myopia	
	4 ml/kg	55 weeks	– severe myopia with "ring formation"	
monkey	90 %			[18]
	3–10 g/kg	29 weeks	– increased diuresis, haemosiderin deposits in the liver, spleen and lymph nodes	

* animals were completely immersed in the solution

Application of 90 % solutions or the undiluted substance to the intact or scarified skin of rabbits led to mild oedema, erythema and hypersensitization [18]. Dogs reacted immediately to 60 %, 90 % or 100 % DMSO solutions with local redness and heat and after repeated applications, like primates, with hyperaemia and desquamation of the epidermis at the application site [18]. Pigs tolerated treatment with 50 % or 90 % DMSO for 58 weeks without effects [18].

In the Draize test DMSO was not irritating in the rabbit eye [18]. The intracutaneous sensitization test in guinea pigs yielded negative results [18].

4 Reproductive and Developmental Toxicity

Female *mice* were given daily oral doses of 5–12 g/kg (50 % solution) from day 6 to day 12 of gestation. There were no malformations in the progeny. The same treatment administered intraperitoneally led to limb malformations, anencephaly and coelosomy [15].

Oral application of 5 ml/kg to male and female *rats* during the 4 days before mating and during the entire gestation period led to no visible changes in the progeny [16].

In the progeny of rats which had been given 8–10 ml/kg i.p. (50 % solution) from day 6 to day 12 of gestation, malformations were seen in jaw and tail and in the central nervous system as well. 10 ml/kg was a lethal dose for 30 % of the dams [15]. On day 13 of gestation in rats, a single intraperitoneal injection of a 40 % DMSO solution at a dose of 1 ml/kg did not cause malformations in the progeny [23]. Subcutaneous injection of 10.25 ml/kg on day 8, 9 or 10 of gestation did not result in malformations but significantly increased the number of foetal resorptions [24].

An intraperitoneal dose of 5.5 g/kg given to *hamsters* on day 8 of gestation induced in the progeny malformations of the central nervous system [25]. Likewise, intravenous doses of 2.5 or 5 g/kg and intraperitoneal doses of 5.5 or 8.25 g/kg induced exencephalus, fused ribs, microphthalmia, limb malformations and cleft lip in hamster foetuses [26, 27].

In the *rabbit* neither oral treatment with 5 g 50 % DMSO per kg nor subcutaneous administration of 4 g/kg at the same concentration, in both cases from day 6 to day 14 of gestation, had significant effects on the frequency of abortions or malformations or on the foetal weight [15].

5 Genotoxicity

DMSO is not mutagenic in the Ames test [28] or in the test for point mutations in CHO cells (HGPRT locus) [29] or in L5178Y cells (TK locus) [30]. DMSO induced mutations, however, in *Saccharomyces cerevisiae* [31, 32].

In vivo an increase in the frequency of chromosome aberrations (chromatid breaks) in the bone marrow of rats was observed after daily intraperitoneal application of 5 ml/kg

of a 1 %, 10 %, 50 % or 100 % preparation of DMSO for 5 days. The results suggest that DMSO caused disintegration of the chromosome structure, possibly as a consequence of its primary cytotoxic properties [33].

DMSO did not induce sex-linked recessive lethal mutations in the male germ cells of *Drosophila melanogaster* [34, 35], or aneuploidy in the oocytes or somatic mutations [36].

In mice intraperitoneal administration of high doses of DMSO (1/8 to 1/2 of the LD_{50}) produced DNA single strand breaks in the kidneys but not in the lungs, liver, spleen, testes or brain. The authors of this study do not exclude the possibility that cytotoxic effects of DMSO lead to the physiological breakdown of DNA [37].

6 Carcinogenicity

The effects of DMSO on the tumorigenic activity of dimethylbenz[α]anthracene (DMBA) was investigated in rats. Two groups of 50 male Sprague-Dawley rats were given 20 mg DMBA by gavage. In addition the animals received 50 ppm DMSO in the drinking water beginning in the first group 3 days before and in the second group 3 days after the DMBA administration. A third group received only DMSO in the drinking water. DMSO had no effect on the latency of the tumours induced by DMBA nor on the tumour frequency. DMSO administered alone did not increase the tumour frequency above that in the control group [38].

In ICR/Ha Swiss mice, dermal application of 0.1 ml DMSO, 3 times weekly during a period of 400 days, induced no skin tumours [39]. Initiation-promotion studies based on the skin tumour model were carried out with DMSO in mice. The animals were treated twice weekly with 125 mg benzo[α]pyrene dissolved in 40 µl DMSO or acetone and applied dermally. The number of skin tumours was doubled when DMSO was used as the solvent. In another group tumour initiation was carried out with 7,12-dimethylbenzanthracene dissolved in DMSO. Without promotion treatment the tumour frequency was unchanged relative to that in the controls. Promotion treatment with a solution of phorbol myristate in DMSO reduced the frequency of skin tumours [40].

The results of the initiation study with benzo[α]pyrene can be ascribed to the penetration promoting effects of DMSO. There is controversy as to the significance of the results of the other studies.

7 Manifesto (MAK value, classification)

DMSO has a relatively low vapour pressure so that there is little risk of adverse effects caused by DMSO inhalation during use at normal temperatures. More precise risk estimation is not possible because of the very limited number of studies of inhalative exposure to DMSO. There are no data available for blood levels after pulmonary DMSO intake. Therefore it is not possible to extrapolate the results obtained after oral or parenteral administration. It is likely, however, that inhaled DMSO is rapidly absorbed in the lungs.

Relatively well documented studies are available on the local effects of DMSO on the skin and on the systemic effects after dermal application. It may be deduced from clinical studies that skin contact with concentrated preparations should be avoided. In individual cases, skin changes can be expected after contact with solutions containing only 15 % DMSO.

Repeated dermal application of 1 g/kg body weight induces central nervous symptoms in man. Doses of about 0.5 g/kg are tolerated without effects on the central nervous system and without changes in haematological or clinical chemical parameters. Lens changes, a sensitive parameter in animal studies, do not develop in man.

A final assessment of the teratogenic potential of DMSO is not possible because doses and exposure conditions which are relevant for man have not been studied. Since embryotoxicity and malformations are observed in animals only after oral or parenteral administration of extremely high doses and since adverse effects are not known in exposed humans, there is thought to be very little risk of embryotoxic or foetotoxic damage in pregnant women.

DMSO does not induce point mutations in bacteria or in cultured mammalian cells. The clastogenic effects and the induction of DNA single strand breaks are very likely a result of the cytotoxicity of the DMSO doses used. The positive results obtained in yeast cannot yet be explained.

There are no valid carcinogenicity studies with DMSO. The results which are available provide no evidence of carcinogenic effects. It is, however, important to avoid simultaneous exposure to DMSO and carcinogenic substances at the workplace (substances from Sections III A 1 and A 2). Generally speaking, the absorption-promoting effects of DMSO can be relevant with many substances. For this reason DMSO requires the designation "H".

The available data is insufficient for the establishment of a MAK value for DMSO. There is not sufficient information as to the effects of inhaled DMSO nor have concentration measurements been carried out at the workplace. Therefore DMSO is included in Section II b of the List of MAK Values.

8 References

1. Neumüller, O.-A. (Ed.): *Römpps Chemie-Lexikon, 8th ed., Vol. 2,* p 970, Franckh'sche Verlagshandlung, D-7000 Stuttgart, 1981
2. Brayton, C. F.: *Cornell Vet. 76,* 61 (1986)
3. Rubin, L. F., K. C. Barnett: *Ann. N. Y. Acad. Sci. 141,* 333 (1967)
4. Rubin, L. F.: *Ann. N. Y. Acad. Sci. 411,* 6 (1983)
5. Kligman, A. M.: *J. Amer. med. Ass. 193,* 140 (1965)
6. Sulzberger, M. B., T. A. Cortese, L. Fishman, H. S. Wiley, P. S. Peyakovitch: *Ann. N. Y. Acad. Sci. 141,* 437 (1967)
7. Swanson, B. N.: *Rev. clin. basic Pharmacol. 5,* 1 (1985)
8. Brobyn, R. D.: *Ann. N. Y. Acad. Sci. 243,* 497 (1975)
9. Hockwin, O., H. R. Koch: *Arzneimittelnebenwirkungen am Auge,* Fischer, Stuttgart, New York, 1977
10. Hucker, H. B., J. K. Miller, A. Hochberg, R. D. Brobyn, R H. Riordan, B. Calesnick: *J. Pharmacol. exp. Ther. 155,* 309 (1967)
11. Layman, D. L., S. W. Jacob: *Life Sci. 37,* 2431 (1985)

12. Willhite, C. C., P. I. Katz: *J. appl. Toxicol. 4,* 155 (1984)
13. Smith, E. R., Z. Hadidan, M. M. Mason: *Ann. N. Y. Acad. Sci. 141,* 96 (1967)
14. Rosenkrantz, H., Z. Hadidan, H. Seay, M. M. Mason: *Cancer Chemother. Rep. 31,* 7 (1963)
15. Caujolle, F. M. E., D. H. Caujolle, S. B. Cros, M. M. J. Calvert: *Ann. N. Y. Acad. Sci. 141,* 110 (1967)
16. Caujolle, F. M. E., D. H. Caujolle, H. Boysson, M. M. Calvert: *C. R. Acad. Sci. (Paris) 258,* 2224 (1964)
17. Sommer, S., G. Tauberger: *Drug Res. 14,* 1050 (1964)
18. Günzel, P.: Personal communication to the author, 15.7.1988
19. Barnett, K. C., P. R. B. Noel: *Nature (Lond.) 214,* 1115 (1967)
20. Wood, D. C: *Science 155,* 404 (1967)
21. Uramura, T.: *Igaku Kenkyu 30,* 2235 (1960)
22. Brown, V. K., J. Robinson, D. E. Stevens: *J. Pharm. Pharmacol. 15,* 688 (1963)
23. Hemsworth, B. N.: /. *Reprod. Fertil. 17,* 325 (1968)
24. Juma, M. B., R. E. Staples: *Proc. Soc. exp. Biol. (N. Y.) 125,* 567 (1967)
25. Marin-Padilla, M.: *Proc. Soc. exp. Biol. (N. Y.) 122, 111* (1966)
26. Ferm, V. H.: *J. Embryol. exp. Biol. Med. 16,* 49 (1966)
27. Ferm, V. H.: *Lancet I,* 208 (1966)
28. McCann, J., E. Choi, E. Yamasaki, B. N. Ames: *Proc. nat. Acad. Sci. (Wash.) 72,* 5135 (1975)
29. Amacher, D. E., I. Zelljadt: *Mutat. Res. 136,* 137 (1984)
30. Amacher, D. E., S. Paillet, G. N. Turner, V. A. Ray, S. Salsburg: *Mutat. Res. 72,* 447 (1980)
31. Callen, D. F., R. M. Philpot: *Mutat. Res. 45,* 309 (1977)
32. Yee, B., S. Tsuyumu, B. G. Adams: *Biochem. biophys. Res. Commun. 49,* 1336 (1972)
33. Kapp, R. W., B. E. Eventoff: *Teratog. Carcinog. Mutag. 1,* 141 (1980)
34. Alexander, M. L.: in Wheeler, M. R. (Ed.): *Studies in Genetics,* p 505, University of Texas, USA, 1966
35. Mollet, P., U. Graf, F. E. Würgler: *Arch. Genet. 47,* 184 (1974)
36. Traut, H.: *Environm. Mutag. 5,* 273 (1983)
37. Walles, S. A. S., K. Erixon: *Carcinogenesis 5,* 319 (1984)
38. Fletcher, W. S., D. L. Dennis: *Ann. N. Y. Acad. Sci. 141,* 214 (1967)
39. Loewengart, G., B. L. van Duuren: *J. Toxicol. environm. Hlth 2,* 539 (1977)
40. Jacobi, W. T, H. S. Weiss: *J. nat. Cancer Inst. 77,* 983 (1986)

completed 16.10.1989